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EXAMINER	
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ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,760	HASSON ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2008 and 19 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-23,29,39,42-46,49 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28,30-38,40,41,47,48,50,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/10/07,10/6/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 11/6/08 to the claims have been entered. Claim 50 has been amended in this reply. Claim 53 has been added. No claims were canceled. Claims 1-53 remain pending in the current application.

Election/Restrictions

Applicant's election with traverse of Group II, claims 24-41, 47, and 48, in the reply filed on 11/6/08 is acknowledged. The traversal is on the ground(s) that Groups II-IV are unified by a special technical feature (11/6/08 Reply, page 11). This is not found persuasive because 37 C.F.R. 1.475 sets forth specific guidelines for placing claims into Groups. Group III is drawn to transdifferentiated cells, specifically endodermal cells, which were certainly known in the art at the time of filing (e.g., liver cells). Group IV is drawn to hormones per se, e.g. insulin, which were also known at the time of filing. The manner in which these products are made cannot impart patentability in the absence of evidence to the contrary. See M.P.E.P. § 2113. The requirement is still deemed proper and is therefore made FINAL. It is noted that the 11/6/08 amendment to claim 50 cause claims 50-53 to be included in Group I.

Applicant's election of the species "conditions wherein said cells are cultured in the presence of a copper chelator," "hematopoietic cells," "SCF," "expression of CD133," "FLT3 ligand," "granulocyte colony stimulating factor," "not carrying any exogenous DNA," "insulin," and "insulin" in the reply filed on 11/6/08 is acknowledged. Applicant's election of the species "diabetes" in the reply filed on 2/19/09 is also

acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement in either case, these elections have been treated as elections without traverse (MPEP § 818.03(a)).

Claims 1-23, 42-46, and 49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/6/08. Claims 29, 39, and 51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on 11/6/08 and 2/19/09.

Examination on the merits will commence at this time on claims 24-28, 30-38, 40, 41, 47, 48, 50, 52, and 53 ONLY, to the extent they read on the elected species where applicable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-28, 30-38, 40, 41, 47, 48, 50, 52, and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expanding and differentiating embryonic stem (ES) cells and inducing expression of a few proteins expressed by hepatocytes, does not reasonably provide enablement for methods of expanding and transdifferentiating any given stem or

progenitor cell into a stem call that has any particular endodermal cell phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are broad and indefinite in scope, mostly describing the culturing conditions of the method steps using functional language (see rejections under 35 U.S.C. § 112, second paragraph, below). In the interest of compact prosecution, the examiner has interpreted the claims reasonably and considered the enablement requirement. The independent claim, which will be discussed first, may be broadly interpreted as being drawn to a method comprising (a) obtaining a population of stem cells from a tissue other than one that originates from the embryonic mesoderm; (b) culturing these stem cells in the presence of a copper chelator such that they may proliferate and do not differentiate; and (c) inducing expression of endodermal cell markers in these stem cells to yield a cell with an endodermal cell phenotype (page 65).

However, several aspects of this method fail to be fully enabled by the specification, even when it is considered in view of the art.

First, the explicit definition of "stem cell" at page 22, lines 4-14, is extremely narrow, limited to "pluripotent cells," i.e., non-committed cells that have the potential to yield any type of cell in the body. Pera (2001, *Current Opinion in Genetics and Development* 11: 595-599; reference U) teaches that around the time of the invention, cells postulated as being pluripotent included embryonic stem (ES) cells and embryonic germ (EG) cells (page 595, e.g.). Writing years after the instant filing, Turnpenny et al. (2006, *Stem Cells* 24: 212-220; reference V) indicate that skilled artisans have not reached consensus as to whether EG cells are truly pluripotent (pages 217-218). Even more recently, Ratajczak et al. (2008, *Journal of Autoimmunity* 30:151-162; reference W) indicated that pluripotent cells isolated from non-embryonic sources were not known (pages 153-155 and Figure 3). Taken together, the art indicates that the only truly pluripotent stem cell is an ES cell (at least, at the time of the invention and through 2008); applicant has provided no guidance for isolating "stem cells" as defined at page 22 from any non-endodermal tissue (the definition at page 64, lines 27-29 is noted) other than early embryonic tissue.

Even if the starting material were limited to ES cells, the specification would still fail to enable a method of making cells with any given "endodermal cell phenotype." The definition of this term at page 65, lines 28-30, is extremely broad, including any "identifying" morphological, genetic, or metabolic property of any endodermal cell, i.e. any cell from any tissue that originates from endoderm (see page 64, lines 27-29). The

genus of endodermal cells is broad and diverse with respect to structure and function and includes hepatocytes and pancreatic islet cells as well as cells that make up the alveoli of the lungs, thymocytes (which give rise to T cells), and thyroid hormone-producing cells. The specification points out a few markers of hepatocytes (page 66, lines 2-4) and a few markers of pancreas (page 66, lines 4-9) but provides no guidance as to which morphological or metabolic properties are identifying properties of these tissues. Furthermore, the specification provides no guidance for identifying morphological, genetic, or metabolic properties for other endodermally-derived tissues and is silent as to methods that specifically promote the production of cells with the phenotypes of other endodermal cells (i.e., cells other than hepatocytes or pancreatic beta cells).

Applicants present several working examples, but none of them appears to embody the claimed method. In one example, multipotent stem cells (which are not synonymous with pluripotent stem cells) are isolated from umbilical cord blood based on their expression of CD133 and then cultured under one of two sets of conditions (so-called "HSC conditions" and "hEndSC-positive conditions") that include incubation with tetraethylenepentamine (TEPA), a copper chelator; this example also includes a teaching in which “hEnd stem cells” are cocultured with damaged liver tissue, but the specification does not clearly define these "hEnd stem cells" in terms of any structural or physical properties, e.g., genetic, morphological, or metabolic characteristics (pages 82-84 and 90-91). The specification also includes an embodiment in which hepatocytes, which are both endodermally-derived and not stem cells (and therefore cannot

reasonably be considered to be a starting material for the claimed method), are cultured in TEPA and shown to proliferate and yield oval cells (hepatic stem cells; pages 84-85 and 88). The specification includes several embodiments in which CD133-expressing cells are transplanted into mice, thereby reconstituting their insulin-producing activity (pages 85-86 and 88-90) but gives no information as to the properties of these implanted cells prior to administration.

The specification includes no working examples in which stem cells according to applicant's own definition are expanded by contact with a copper chelator and then induced to yield any cell with any endodermal cell marker. Example III (pages 90-91) details the results of an experiment in which multipotent stem cells are grown under conditions that appear to promote their ability to replace pancreatic islet function, but this example is silent as to the expression of any pancreatic marker of the cells yielded by the *ex vivo* culturing. There is no indication that the method employed in Example III yields "stem cells expressing endodermal cell markers" or, indeed, any cells that express markers characteristic of any endodermal tissue.

While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-28, 30-38, 40, 41, 47, 48, 50, 52, and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The language of a claim must make it clear what subject matter the claim encompasses to adequately delineate its "metes and bounds." See, e.g., *In re Hammack*, 427 F 2d. 1378, 1382, 166 USPQ 204, 208 (CCPA 1970); *In re Venezia* 530 F 2d. 956, 958, 189 USPQ 149, 151 (CCPA 1976); *In re Goffe*, 526 F 2d. 1393, 1397, 188 USPQ 131, 135 (CCPA 1975); *In re Watson*, 517 F 2d. 465, 477, 186 USPQ 11, 20 (CCPA 1975); and *In re Knowlton,* 481 F 2d. 1357, 1366, 178 USPQ 486, 492 (CCPA 1973). The courts have also indicated that before claimed subject matter can properly be compared to the prior art, it is essential to know what the claims do in fact cover. See, e.g., *In re Steele*, 305 F 2d. 859, 134 USPQ 292 (CCPA 1962); *In re Moore*, 439 F 2d. 1232, 169 USPQ 236 (CCPA 1969); and *In re Merat*, 519 F 2d. 1390, 186 USPQ 471 (CCPA 1975). In this case, the claims are so indefinite as to preclude a substantive search by the examiner for at least the reasons set forth below.

Step (a) of claim 24 is not commensurate in scope with the preamble of the claim. The preamble limits the stem cells to “non-endodermally derived stem cells,” while step (a) refers to “stem and/or progenitor cells.” Because the preamble of claim 24 explicitly requires that transdifferentiation occurs, it is not clear whether the cells of step (a) are the cells recited as the starting product in the preamble or not. Furthermore, the definition at page 22, lines 4-14, clearly limits the term “stem cells” to “pluripotent cells”

or “the earliest renewable cell population responsible for generating cell mass in a tissue or body and the very early progenitor cells, which are somewhat more differentiated, yet are not committed and can readily revert to become a part of the earliest renewable cell population,” i.e., cells that have the potential to yield any tissue in the body, but the limitation “progenitor cells” is far broader, encompassing any cell that can give rise to a cell type that is different from itself. Because both "stem cells" and "stem and/or progenitor cells" are recited in the claim, the scope of the starting material is indefinite.

Step (b) of claim 24 requires culturing stem and/or progenitor cells (hereinafter “SC”) under “conditions allowing for cell proliferation,” but these conditions are not particularly described in the claim. It is also not clear whether the conditions of step (b) must promote SC proliferation or whether they must merely permit it.

Lines 29-31 of claim 24 require that step (b) “expand the SC while at the same time substantially inhibiting differentiation of the SC,” which is confusing because the “thereby” clause merely recites a result of the conditions of step (b) without setting structural or physical limits on those conditions. Furthermore, it is not clear what degrees of inhibition would be considered “substantial” and which would not.

Step (c) of claim 24 requires “inducing enrichment of said SC for stem cells expressing endodermal cell markers,” which is unclear for several reasons. First, the nature of the induction is not pointed out; it is not clear whether step (c) is a positively recited active method step and, if so, what processes it is intended to include and exclude. Furthermore, it is not clear which markers are within the scope of “endodermal

cell markers" and which are not. The end point of step (c) is not clear, and neither is the means by which it is to be accomplished.

Lines 32-33 and 34-35 of claim 24 appear to conflict with each other, since the former requires that step (c) yield stem cells expressing endodermal cell markers and the latter that step (c) yield stem cells "having an endodermal cell phenotype." The definition of "endodermal cell phenotype" at page 65, lines 28-30, of the as-filed specification includes morphological and metabolic properties, not just genetic changes. In other words, a cell having an "endodermal cell phenotype" according to that definition may not necessarily express any so-called "endodermal cell markers." In any case, the scope of the limitation "endodermal cell phenotype" is queried, since the definition at page 65 does not clearly limit which characteristics are "identifying" and which are not.

The term "stem cell having an endodermal cell phenotype" is queried. Finally, as discussed above, the phrase "stem cells" is explicitly defined at page 22 as being limited to non-committed early progenitor cells; it is not clear how a "stem cell" that is not committed to any lineage can simultaneously have an "endodermal cell phenotype," given that these phenotypes are defined at page 65 as being identifying characteristics of endodermal cells, i.e. those that would distinguish endodermal cells from all other cell types. The phrase "stem cells expressing endodermal cell markers" and "stem cells having an endodermal cell phenotype" simultaneously require that the cells be completely non-committed to any lineage and that they be sufficiently differentiated as to possess properties of differentiated endoderm. The product of the method is not particularly defined.

Clarification of all of these points is required. Because claims 25-28, 30-38, 40, 41, 47, 48, 50, 52, and 53 depend from indefinite claim 24 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claims 28 and 30 require that the method of claim 24 "further comprise" selection steps, but it is not clear how these additional steps relate to the method of claim 24. It is not clear, for example, whether these selection steps may be carried out before, after, or at any given time during the method of claim 24. Clarification is required.

Claims 31 and 33 require that the selection of claims 30 and 32, respectively, be "affected [*sic*] by CD133," but the claim fails to set forth any active steps by which selection is effected. Clarification is required.

Claim 47 requires continued culture of the cells after the steps of claim 24 "whereby an endocrine hormone may be produced." First, the conditions encompassed by the "whereby" phrase are not particularly pointed out in the claim. Second, it is not clear whether endocrine hormone production is a necessary effect of the continued culturing, since the "whereby" limitation only requires that a hormone "may be" produced. Clarification is required.

Claim 50 requires that the method of claim 24 be "used for treating or preventing a liver or pancreatic disease" but fails to include any method steps that would lead to treatment or prevention and, indeed, completely omits any subject for the treatment or prevention. Claim 50 does not require, e.g., administering any cells or products to any individual. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 52 is in improper Markush form; a Markush group should be in the form "a disease selected from the group consisting of A, B, **and** C". Currently, it is not clear which species are included in the Markush group and which are not.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 50, 52, and 53 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). In this case, claim 50 recites a "use" of the method of claim 24 but fails to point out any subject on which the method is used or any steps that are constituted by the use.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651